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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/632,187 | 07/30/2003 | Jurgen Engel | 103832-477-NP | 9817 |

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| EXAMINER | |
|---|---|
| GEMBEH, SHIRLEY V | |
| ART UNIT | PAPER NUMBER |
| 1618 | |
| MAIL DATE | DELIVERY MODE |
| 04/10/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/632,187 | ENGEL ET AL. | |
| | Examiner | Art Unit | |
| | SHIRLEY V. GEMBEH | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5 and 8-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendment*

1. The response filed on **1/29/09** has been entered.

**2.** Applicant's argument's filed 1/29/08 has been fully considered but they are not deemed to be persuasive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1-5 and 8-13 are pending in this office action. Claim 13 is newly added.

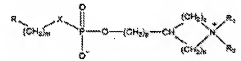
5. The rejection of claims 5 and 8 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description (New Matter rejection) is withdrawn due to the amendment to cancel the term "excluding cyclophosphamide" from the claims.

6. The rejection of claims 1, 4-5 and 8-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description is withdrawn due to the amendment of the claims, specifically the cancellation of the term "prodrugs".

7. The rejection of claim 7 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description is withdrawn due to the cancellation of claim 7.

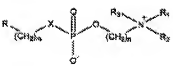
8. Claims 1-3 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard et al. (1993) in view of Goodman and Gilman for the reasons made of record in Paper No. 20080729 and as follows.

The claims recite a method of treating mammary carcinoma comprising administering an alkylphosphocholine of formulae



Formula II

and



Formula I

in combination with an approved antitumor agent e.g. carboplatinum, oxaliplatinum etc, wherein the alkylphosphocholine is administered before or prior to the approved antitumor agent.

Applicant argues in summary that Hilgard teaches the use of miltefosin in combination with cyclophosphomide for the treatment of mammary carcinoma and discloses by references the combination with cisplatin derivatives. Also Applicant argues that absent understanding of the mechanism of drug resistance and drug activity, one of ordinary skill in the art would have no obvious way of selecting effective combination of alkylphophocholines and other antitumor agents. In their argument Applicant agrees that Calabresi teaches properly selecting combinations of drugs may be useful.

In response Applicant's argument is found not persuasive because page 93 (left col. last 3 lines) specifically teach that miltefosine (same compound with the claimed invention) showed no effect at doses given, whereas in combination with a platinum complex it greatly enhanced the antitumor effect. In that same paragraph, Hilgard also teaches that when using an *in vivo* mouse model there was synergy between miltefosine and a new cisplatinum derivative. Whether Hilgard discloses via reference the combination of miltefosine and cisplatinum is irrelevant because Hilgard regards the teaching as important, thus making the teachings of record obvious.

Because Hilgard teaches synergistic combination of the same drug with the same class of drugs, one of ordinary skill in the art would have been motivated to employ Hilgard's teaching even without the knowledge of drug interaction because it has been known in the art that both miltefosine and cisplatinum derivatives have both been employed in the treatment of mammalian carcinoma, and therefore use of both drugs would have been obvious to one of ordinary skill in the art to employ. Calabresi further embraces the concept of synergy between two drugs.

9. Claims 1-5 and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard[1] et al. (1993) in view of Goodman and Gilman further in view of Hilgard[2] et al (1996) and further in view of Principe et al. (1992) for the reasons made of record in Paper No. 20080729 and as follows.

Applicant should note that the limitations of instant claim 13 has been addressed previously in the last office action of record as the limitations are the same as instant claim 1.

Applicant's argument with regards to Hilgard and Calabresi are as applied above.

Further Applicant argues that not every combination of drugs will be effective against all types of tumor, and that Principe at page 581, 2nd paragraph teach that in HT29 cells a supra-additive effect is observed with the combination of ether phosphoiipid ET-I 8-OCH3 and MMC, ADM, *CDDP*, 13LM, VLB, and VP-16. However, in A427 cells, a supra-additive effect is observed with the combination of ether phospholipid ET- 1 8-$OCH_3$ and MMC, ADM., etc but a sub-additive effect is observed with the combination of ether phospholipid ET- 1 8-$OCH_3$ and VLB or VP-16, and that one cannot predict how a particular cell type will react to a particular combination of agents.

In response, see ¶ # 8 for comments concerning Hilgard and Calabresi. As to the assertion that one cannot predict how a particular cell type will react to a particular combination of agents, this is not found persuasive because the primary reference Hilgard teaches the combination of the drugs for the treatment of the same type of cancer. Whether or not Principe teaches that different cells may differ is irrelevant because the same cancer cells to be treated are compared. It is further known to one in the art that different combinations of drugs are effective for more than one type of cancer cell. One of ordinary skill in the art would have been motivated to combine Hilgard, Calabresi and Principe and administer an adjuvant therapy of alkylphospholipid

(same class of compounds) with anticancer agent such as cisplatin because the cited prior art Hilgard[1], Hilgard[2] and Principe teach the use of antineoplastic agents with the drug. Also based on the disease, these antineoplastic agents can be combined to treat a specific disease as taught by Goodman and Gilman.

Careful consideration has been given to Applicant's argument but found not persuasive for the reasons given and already of record.

10. Claims 2, 7 and 10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard et al., (1993) in view of Stekar et al., (1995) for the reasons made of record in Paper No. 20080729 and as follows.

Applicant argues that both Hilgard and Stekar references disclose the use of miltefosin in combination with cyclophosphamide and cisplatin but fail to teach any other combinations.

This, however, is found not persuasive because Hilgard teaches the combination of miltefosin with cisplatin showed considerable therapeutic synergy, and therefore meets the current claim limitations. Cisplatin is a platinum based drug, and one of ordinary skill in the art would expect the same type of success seen with cisplatin if cisplatin is substituted with oxaliplatinum or carboplatinum, which are platinum-based chemotherapy drugs in the same family as cisplatin. As to the cancellation of cyclophosphamide, since Stekar teaches the combination of the drug miltefosin and Hilgard teaches a combination with cisplatinum, it would have been obvious to one of ordinary skill in the art to substitute cis-platinum with a platinum based

chemotherapeutic agent in combination with miltefosin. As to the argument that the combined use might lead to synergistically enhanced detrimental side effects, no such limitation is claimed. The claims only call for a combination of the agent's miltefosin and an antitumor substance. Whether they cause enhance detrimental side effects or not is not part of the claims, nor is the mechanism of action of the alkylphosphocholine. Based on the above discussion, the rejection is maintained as in the last office action of record.

Applicant's amendment did not overcome the rejected claims.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. V. G./
Examiner, Art Unit 1618
3/30/09

/Robert C. Hayes/
Primary Examiner, Art Unit 1649